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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,582	01/23/2004	Kai Licha	SCH-2208	3021

23599 7590 04/30/2008

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ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
04/30/2008	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/762,582
Filing Date: January 23, 2004
Appellant(s): LICHA ET AL.

Csaba Henter
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 28, 2008 appealing from the Office action mailed July 26, 2007.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

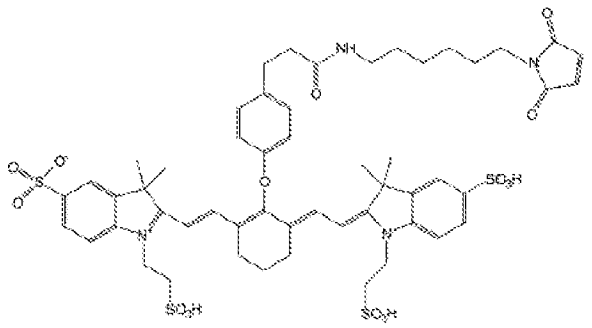
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

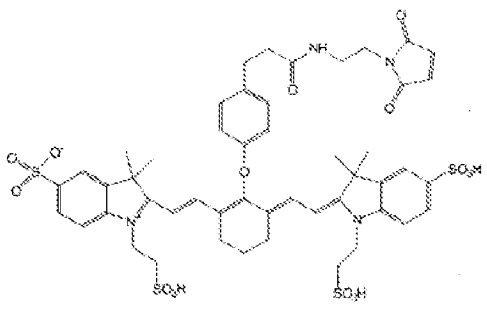
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over ZAHEER (PTO-1449, 10/1/04; cite #3: Mol. Imaging. (2002) vol. 1, No. 4, pages 354-364) in view of ROSENBLATT (PTO-892, 12/30/05; M. Chorev et al. Int. J. Peptide Protein Res. (1992) Vol. 40, pages 445-455) or CHOREV (PTO-892, 12/30/05; US Patent 5,242,680).

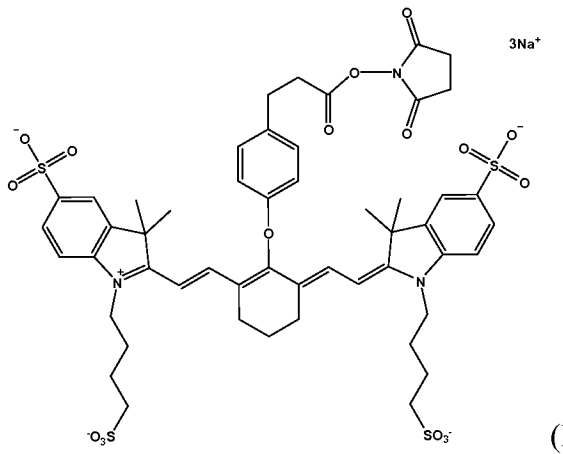
The instant claims are drawn to fluorescent probes with the structures of the two species:

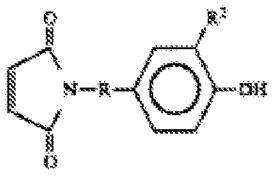
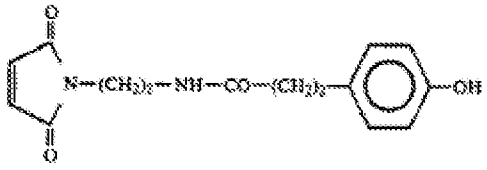
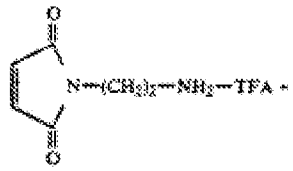
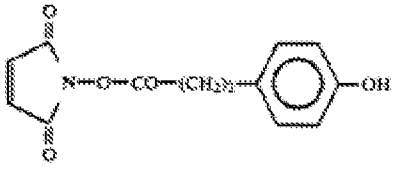
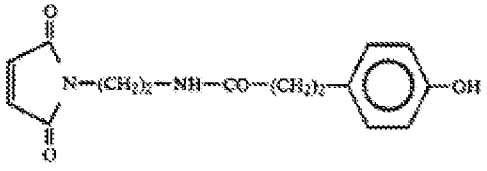


and



and the genus embracing them.

Zaheer teaches the compound:  (Figure 1, page 357).

Chorev teaches the maleimido ligand generically:  (column 2), where R can be $(CH_2)_n$-NHCO-$(CH_2)_m$ and R^2 can be H, n and m are each 0-2, and further teaches the compound:  (column 3) and the reaction of  VII (column 5) with the succinimidyl ester  to form the compound:  .

Chorev additionally teaches that that the maleimido has high specificity towards sulfhydryl and forms a stable thio-ether bond and sulfhydryl has high reactivity towards maleimido moieties (column 2, lines 12-30). Chorev teaches the reactivity of the maleimido towards sulfhydryl groups (e.g. Chorev at columns 5 and 7) and that it is used for labeling of proteins.

The differences between that which is claimed, and that which is taught in the prior art is that while Zaheer teaches the core structure of the fluorescent dye having propyl sulfonate groups, Zaheer does not teach the instantly claimed linker or ethyl sulfonate groups.

It would have been obvious to one of skill in the art at the time of the invention to have made the compound of Zaheer with the linker of Chorev in order to make a fluorescent compound that was selective towards sulfhydryl groups.

One would have been motivated to make the fluorescent dye with the linker of Chorev in order to make a fluorescent compound which is more selective towards sulfhydryl groups.

One would have a reasonable expectation for success in making the fluorescent compound of Zaheer with the linker of Chorev, as the core structure and synthetic methods of coupling linkers to fluorescent markers are well known to the artisan.

With regards to the length of the alkyl chains in the sulfonate groups, the MPEP states, "A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d

381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990)." *See* MPEP § 2144.09. Furthermore, MPEP § 2144.09 states in part, "Prior art structures do not have to be true homologs or isomers to render structurally similar compounds *prima facie* obvious. *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979)". In the instant case, one would have been motivated to make the compounds with varying alkyl chain lengths with the expectation that the compounds having close structural similarities, sharing a core structure, and having the same function (as fluorescent dyes), would have similar properties.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35 and 41 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn generally to solvates of the compounds of the invention.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

VIPPAGUNTA (S.R. Vippagunta, et al. Adv. Drug Delivery Rev. (2001) 48, pages 3-26) teaches that, "The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition, but different internal crystal structures, and therefore, possess different physico-chemical properties." (page 4). "Solvates, also known as pseudopolymorphs, are crystalline solid adducts containing solvent molecules within the crystal structure, … giving rise to unique differences in the physical and pharmaceutical properties of the drug. If the incorporated solvate is water, a solvate is termed a hydrate." (page 4).

Vippagunta teaches that, "Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products, while differences in solubility may have implications on the absorption of the active drug from its dosage form, by affecting the dissolution rate and possibly the mass transport of the molecules." (page 4).

Vippagunta teaches that, "It is very important to control the crystal form of the drug during the various drug development, because any phase change due to polymorph

interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics." (page 5).

Vippagunta teaches that there are reversible and irreversible polymorphs (page 6), and polymorphs which are structural or conformational polymorphs (pages 7-11). Vippagunta further teaches that, "The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case." (page 11).

Vippagunta teaches that "Phase changes due to hydration/dehydration and salvation/desolvation of pharmaceutical compounds during processing or in the final product may result in an unstable system that would effect the bioavailability of drug from solid dosage forms. Various types of phase changes are possible in solid-state hydrated or solvated systems in response to changes in environmental conditions… For example, some hydrated compounds may convert to an amorphous phase upon dehydration and some may convert from a lower to a higher state of hydration yielding forms with lower solubility. Alternatively, a kinetically favored but thermodynamically unstable form may be converted during pharmaceutical processing to a more stable and less soluble form." (page 17).

Vippagunta teaches that, "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of

related compounds… There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." (page 18).

(5) The relative skill of those in the art:

The relative skill of those in the art is low with regards to determining which solvates of a compound can be formed.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided for salts of the compounds and making them. However, the specification does not provide examples of making solvates.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above and the high unpredictability in the art with regards to solvates and the inability to make generalizations regarding them, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make solvates of the compounds commensurate in scope with the claims.

Claims 35 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated that, "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated that, "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found

not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the

claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn generally to solvates of compounds.

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art is low, particularly with regards to making solvates, as stated above, being that a particular solvate of a compound cannot be predicted.

(2) Partial structure:

The specification and claims provide for the compound in the solvate, however no structure or chemical entity is provided for as being the solvent molecule in the solvate.

(3) Physical and/or chemical properties and (4) Functional characteristics:

The compound must be a solvated compound and comprise a solvent molecule which thus forms the solvate.

(5) Method of making the claimed invention:

Methods of making a particular solvate are unpredictable and the disclosure provide no guidance or examples on which solvates of which compounds can be made, nor does the specification provide guidance as to selection of solvents which will result in solvates of any compound in the specification.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 35 and 41 is/are broad and generic, with respect to all possible solvate encompassed by the claims. The possible structural variations are limitless to any solvent/solvate molecule. Moreover, the specification is void of any exemplary solvate, and even disclosure of one would not be

sufficient to reflect this variance in the genus of solvents that may form a solvate. While having written description of the compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the solvates of compounds as embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

(10) Response to Argument

In Applicant's Appeal Brief, Applicant addresses the Final rejection, mailed July 28, 2006, as well as the Non-Final action mailed July 26, 2007 in response to the rejection set forth under 35 USC § 103(a). The discussion of the Final rejection mailed July 28, 2006 is not germane to the rejections on Appeal. Applicant argued previously that because 8 references were relied upon, the *prima facie* case of obviousness was/is improper. As stated in the Non-Final Action mailed July 26, 2007 in response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). As Applicant correctly indicates,

the rejection is substantially that which had been previously made, however fewer references were could be relied upon in making the rejection. The number of references presented prior to the rejection on Appeal merely showed that the core structure of the indole-linker-indole was well known to the artisan and had been modified in various ways. As indicated in the Non-Final Action, any of the references could have been relied upon as a 'primary' reference for the rejection set forth under 35 USC § 103(a), however to simplify the issues, a single primary reference was selected.

Claim Rejections - 35 USC § 103

With regards to the rejection set forth under 35 USC § 103(a), in the Non-Final Action mailed July 26, 2007 Applicant reasserts the arguments presented previously that:

(1) the fact pattern in *Jones* is analogous to the instant claims;

(2) the examiner relies upon the instant disclosure as a roadmap, i.e. hindsight reasoning;

(3) Applicant further argues that "Not one single reference generically teaches each and every component of the claimed invention herein and/or even how the pieces of the various compounds should be formulated into a single structure" (emphasis added, page 4);

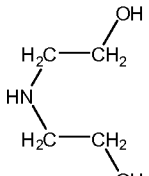
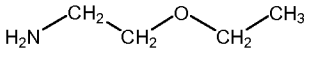
(4) "There is no reason provided in the references for the particular combination alleged" (emphasis added, page 4) and that Chorev would not be considered analogous art; and

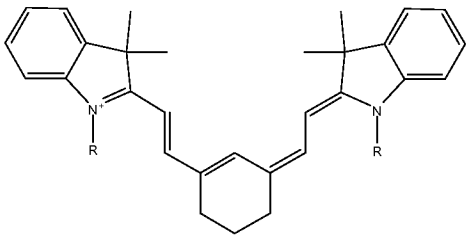
(5) there is no common core in the compounds of the relied references.

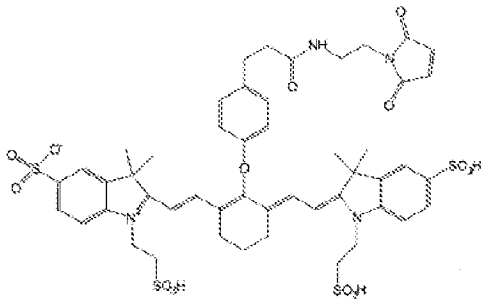
While Applicant's arguments have been fully considered, they have not been found persuasive.

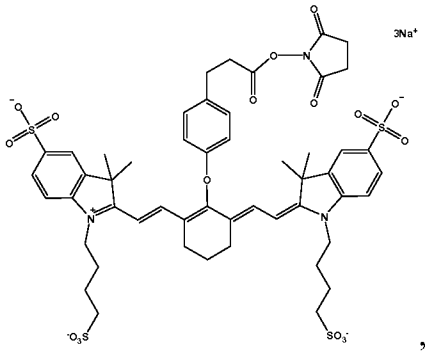
(1) the fact pattern in Jones is analogous to the instant claims. As stated previously, contrary to Applicant's arguments, *Jones* is not analogous to the instant rejection, and provides a

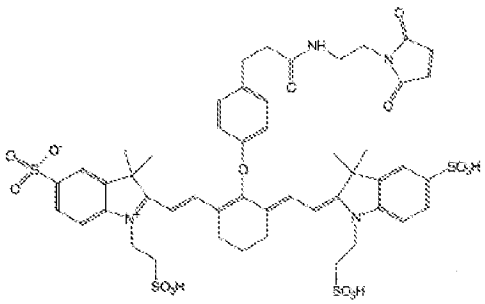
substantially distinct fact pattern which cannot be applied to the claims of the instant Application.

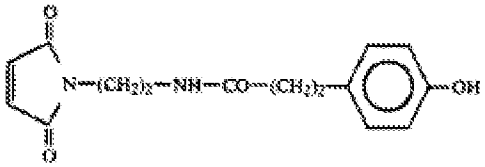
Jones compares two compounds $HOCH_2CH_2NHCH_2CH_2OH$, a secondary amine, which is a dialkyl amine with the structure:  with the compound $NH_2CH_2CH_2OCH_2CH_2OH$, a primary amine, which is a monoalkyl amine with the structure:  , and the issue is connectivity of atoms within a single structure, and the non-obviousness to rearrange the atoms, and not the reliance upon secondary references to bring in the missing elements or how one could extrapolate molecular rearrangement of atoms to reliance upon multiple references under 35 USC § 103.

Here, the compound of Zaheer and the instantly claimed compound share a common core (addressed below in more detail): 

Example of instant claimed compound:  and

Zaheer:  , which differs by missing elements, which are brought in by secondary references, e.g. Chorev, in contrast to *Jones*, which addresses the issue of connectivity of elements which are already present in a molecule. Furthermore, it Appears Applicant is arguing that *Jones* is applicable to the comparison of the instant claims, e.g.

 and the compound of Chorev, e.g.

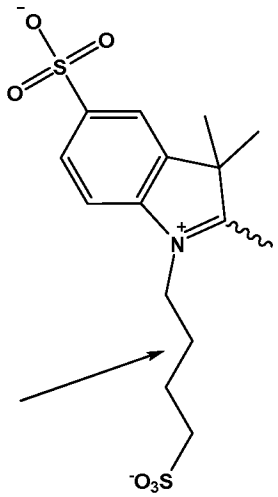
 . Chorev is relied upon to rectify the deficiency of Zaheer, specifically the maleimido linker.

(2) the examiner relies upon the instant disclosure as a roadmap, i.e. hindsight reasoning. In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, contrary to Applicant's opinion, the elements were not selected 'in isolation' or 'pieced together', and the examiner did not rely upon the instant disclosure. The art, as identified by the examiner, provided the knowledge which was within the level of ordinary skill at the time of the invention, and thus set forth a proper *prima facie* case of obviousness. Linkers which are selective towards various moieties, e.g. amines and sulfhydryls, are known to the artisan, as evidenced by the art previously relied upon and of record, and thus selection of a moiety with a known predictable effect, e.g. selectively targets sulfhydryls, is well within the knowledge and skill of the artisan and is not derived from Applicant's disclosure.

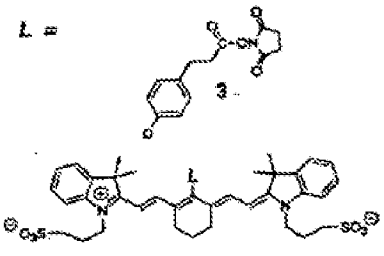
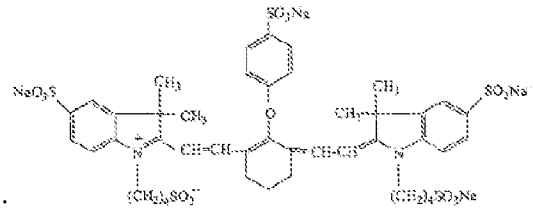
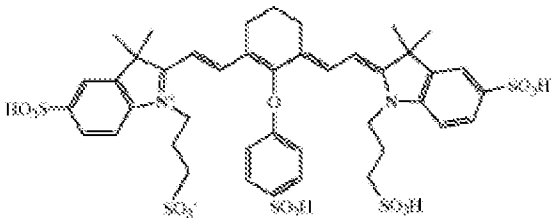
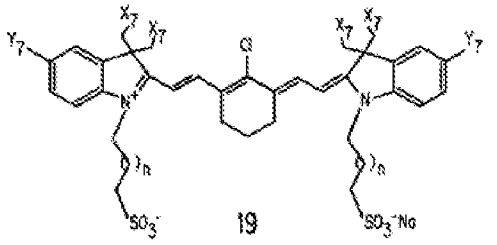
(3) "Not one single reference generically teaches each and every component of the claimed invention herein and/or even how the pieces of the various compounds should be formulated into a single structure." Applicant improperly requires that the reference anticipate the instantly claimed compound (that a single reference teach 'each and every component'), where an obviousness rejection was made. Furthermore, it should be noted that *KSR* forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding

of obviousness (*See Ex Parte Smith*, USPQ2d, slip op. 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR v. Teleflex*, 82 USPQ2d 1396).

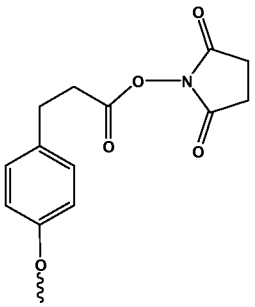
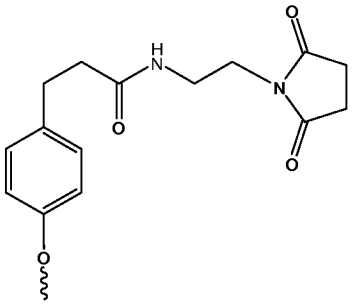
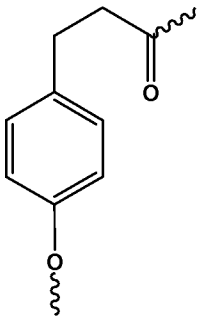
(4) "There is no reason provided in the references for the particular combination alleged" (emphasis added, page 4) and that Chorev would not be considered analogous art. As stated above, *KSR* forcloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness (*See Ex Parte Smith*, USPQ2d, slip op. 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR v. Teleflex*, 82 USPQ2d 1396). Alternative rationales may be relied upon, including (but not limited to) combining prior art elements according to known methods to yield predictable results and simple substitution of one element for another to obtain predictable results. Here, the compound of Zaheer is distinguished by two elements- the alkylsulfonate group chain length and the selection of the linker, both of which are taught in the art and have predictable results.

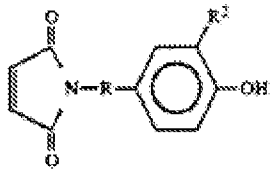


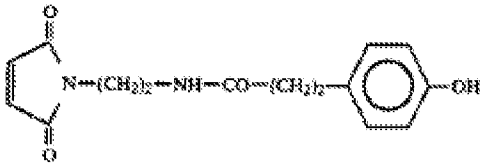
With regards to the alkylsulfonate, , the difference between the instant claims and the teachings of Zaheer is the length of the alkyl chain, where the prior art chain is 4 methylene units and the instant claims are 2 or 3 methylene units. Compounds having

the same core structure with various methylene chain lengths (2-5) are known in the art, and have been cited in previous actions, e.g. Flanagan (PTO-1449, 10/1/04; Bioconj. Chem. (1997) pages 751-756):  ; Miwa (PTO-1449, 10/1/04; WO 00/16810 A1) :  ; and Achilefu (PTO-892, 12/30/05: US Patent 6,733,744 B1):  and  . Thus, with respect to the functionality of the compound as a fluorophore, variation in the number of methylene units of the alkylsulfonate does not adversely affect the ability of the compounds to function as fluorophores. Thus, given there are related compounds having the very same core and varied alkylsulfonate chain lengths, one would have found sufficient motivation in the knowledge available in the art to vary the length of the alkylsulfonate chain between 2 and 5 methylene units. Here, Applicant has provided no

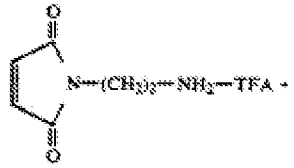
evidence to rebut the argument that the fluorophore would no longer function as a fluorophore, nor has Applicant disclosed in the specification or presented evidence or arguments that there is an unexpected property attained from altering the alkylsulfonate chain length.

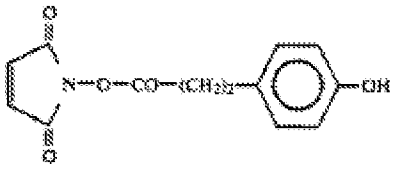
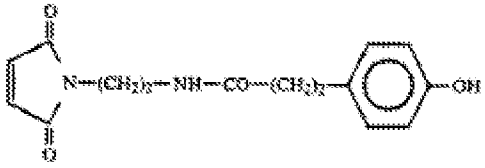
With regards to the linker, the difference between the instant claims and that of Zaheer is the selection of the binding moiety. The linking moiety of Zaheer,  and that of the instant claims, e.g.  share the same core  , differing only by the terminal binding moiety selected.

As discussed above, Chorev rectifies this deficiency and teaches the maleimido ligand generically:  (column 2), where R can be $(CH_2)_n$-NHCO-$(CH_2)_m$ and R^2 can be H, n and m are each 0-2, and further teaches the compound:



(column 3) and the reaction of



VII (column 5) with the succinimidyl ester  to form the compound:  .

The compound of Chorev was used to attach a label, in the case of Chorev a radiolabel, however both the radiolabel of Chorev and the fluorophore of Zaheer are both ways to label compounds, and thus Chorev is, in contrast to Applicant's assertion, analogous art.

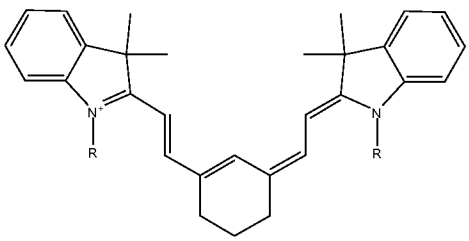
Zaheer shows that the compound is used to selectively tag sulfhydryl groups with a detectable label. Reactivity of the maleimido group with sulfhydryl groups is well known in the art, and thus provides an predictable result that the compound attached to such a ligand will selectively tag sulfhydryl groups. One is merely substituting a known element for another element to obtain a predictable result.

Thus, when taken as a whole, the deficiencies of Zaheer are rectified by both art and knowledge which is readily available in the art to provide predictable results. This is in direct contrast to Applicant's unsupported assertion that, "it is entirely unclear from the references that even if such piecing together would be performed, whether the resultant compounds would have

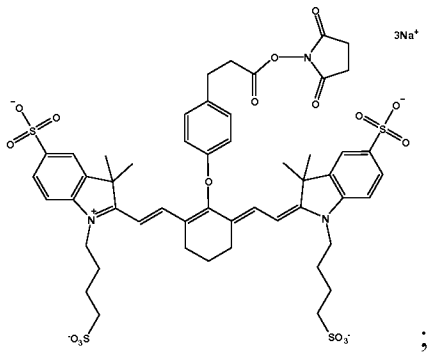
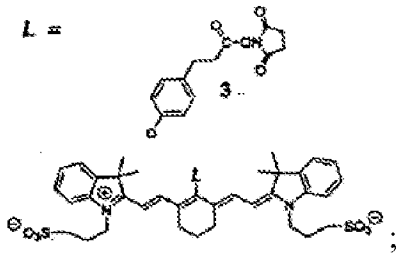
the desired properties. One of ordinary skill in the art would not have an expectation of success based on the teachings of the prior art to prepare compounds with the desired properties." Obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. See, e.g., *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Here, there is a reasonable expectation that the resultant compounds would function as fluorophores, particularly since other compounds sharing the same core structure are known to be fluorophores, and there is a reasonable expectation that the compound would function as a tag/label for sulfhydryl groups, as the reactive moiety is known to bind selectively to sulfhydryls.

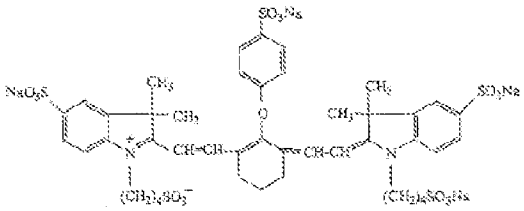
(5) There is no common core in the compounds of the relied references. As discussed above, the compounds relied upon, do indeed, share a common core as set forth by the examiner, which would be immediately recognized by one of skill in the art. Applicant again frames the argument from the perspective that the compound of Chorev (the linker) is the basis for comparison with the instantly claimed compound. In contrast, the examiner has maintained that Zaheer, and other compounds of the art of record, share the common structure. Chorev has been relied upon to rectify the deficiency in Zaheer as to the differences in the linker selected.

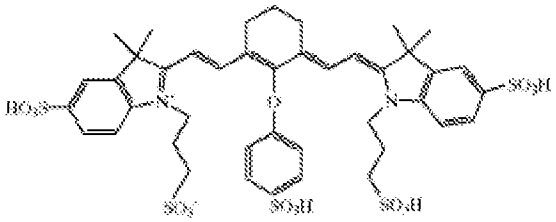
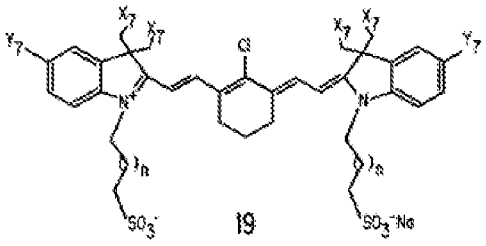
The compounds relied upon previously are depicted graphically to assist in visualizing the clear common core of two indole groups with a common linker having the core:



. The compounds having this core are:

Zaheer:  ; Flanagan:  ;

Miwa:  ; and Achilefu:

 and  . Such

compounds clearly share a significant common core, as discussed, and depicted, above. Here, the compounds of the prior art are highly analogous, sharing a significant core structure, where any one reference could be relied upon as the primary reference. The motivation to form the instantly claimed compounds is derived from the references, to make a compound that is low in toxicity and selective towards sulfhydryl groups.

Thus, when taken as a whole, the instantly claimed compounds are *prima facie* obvious.

Claim Rejections – 35 USC § 112

With regards the rejection under 35 USC § 112, 1st ¶ (enablement), Applicant argues that it would not be an undue burden to make solvates of the compounds of the invention, asserting

that, "there is no basis to doubt objective enablement" (page 6) because, allegedly, "The Examiner has not established any basis to doubt objective enablement." (page 6).

Applicant further states, "One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are enabled, bring them together with various solvents under various conditions and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Any amount of unstability, phase changes, etc., can be determined by routine testing." (page 6).

Respectfully, the examiner disagrees. Contrary to Applicant's assertion, the examiner clearly established a basis to doubt the "objective enablement", through the reference to Vipagunta, which clearly teaches that solvates of compounds cannot be predicted. Thus, there is ample reason to doubt the enablement, and when taken together with the lack of guidance and examples in the instant disclosure, one would clearly be burdened with undue experimentation to make solvates.

While Applicant is correct that *Wands* does allow for experimentation, the key word is 'undue'. MPEP 2164.06 states (in part), "The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988) (*citing In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989)." Here, the art shows that one cannot predict which solvates will form, and the specification is absent any examples, providing only the general statement that solvates are contemplated (page 5, "… and solvates of this compound."). Furthermore, Applicant merely provides unsupported arguments that it would not be a burden to form solvates, and does not even address the issues raised by Vippagunta with regards to the unpredictable nature of solvent formation. Furthermore, it is noted that in rebuttal of the Written Description rejection, Applicant states, "The specification on page 5 recites solvates of the claimed compounds, but does not provide examples of solvates, e.g. by examples of preparation." (page 7).

With regards the rejection under 35 USC § 112, 1st ¶ (written description), Applicant asserts *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006) is appropriate to the question of description. Applicant asserts that in accordance with *Falkner*, "even absent specific examples of solvates, or detailed description of the structures thereof, or even absence of actual reduction to practice of solvates, in view of *Falkner*, there is not an adequate reason provided by the Office Action for the alleged lack of written description rejection." (page 7).

Respectfully, *Falkner* is not germane to the instant rejection, as the fact pattern is substantially divergent. In *Falkner*, Inglis did not provide working examples using the poxvirus, yet provided working examples of using the herpes virus. Additionally, Inglis had not reduced to practice the use of the poxvirus, while having reduced to practice the herpes virus. Further,

Inglis has described the sequence of the herpes virus and critical regions in great detail, and mentions poxvirus without any further description of the sequence or essential elements.

Here, in contrast to *Falkner*, Applicant has provided no description of any example of a solvate, e.g. even the recitation of 'hydrates' is absent from the specification. In contrast, MPEP 2163 states (in part), "What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, e.g., *Eli Lilly*. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces."" Here, the MPEP provides guidance that if the art is unpredictable, a single species is insufficient to provide descriptive support for a genus. In the instant specification and claims, there is no disclosure of any single species of solvate or solvent molecule used, or contemplated, to form a solvate, and because the art is recognized to be unpredictable, one must conclude there is insufficient descriptive support under 35 USC § 112 to support the genus "solvate."

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Andrew D Kosar/

Primary Examiner, Art Unit 1654

Conferees:

/Anish Gupta/

Primary Examiner, Art Unit 1654

Cecilia J. Tsang

/Cecilia Tsang/

Supervisory Patent Examiner, Art Unit 1654